Int. J. Cancer: **118,** 744–748 (2006)

Parental lung cancer as predictor of cancer risks in offspring: Clues about multiple routes of harmful influence?

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The carcinogenic effects of active smoking have been demonstrated for many sites, but the effects of passive smoking and exposures during pregnancy and breastfeeding are less well documented. We examined whether 0–70-year-old offspring of parents with lung cancer are at a risk of cancer that cannot be explained by their smoking or familial risk. It was assumed that known target sites for tobacco carcinogenesis would be affected, if any. The nationwide Swedish Family-Cancer Database with cancers recorded from 1958 to 2002 was used to calculate age-specific standardized incidence ratios (SIRs). Among offspring of affected mothers, increased risks were observed for upper aerodigestive (SIR 1.45), nasal (2.93), lung (1.71) and bladder (1.52) cancers and for kidney cancer (6.41) in one age group. The risk of bladder cancer was found in younger age groups than that of lung cancer. Cancers at many of these sites, but not the kidney or the bladder, were in excess in offspring of affected fathers. Nasal cancer was even increased when either parent was diagnosed with lung cancer; the highest risk was for nasal adenoid cystic carcinoma (7.73). The data suggest that passive smoking during childhood is associated with an increase risk of nasal cancer. For bladder and kidney cancers, a contribution by tobacco carcinogens is implicated through breastfeeding and *in utero* exposure.

Key words: breastfeeding; *in utero* exposure; bladder cancer; kidney cancer; nasal cancer

The devastating health consequences of active smoking are well known.[1,2] The health effects of involuntary smoking are less well known and even the supporting scientific evidence may be limited.[3,4] Scientific data on the possible carcinogenic effects of exposure during pregnancy, breastfeeding and childhood are scanty. The International Agency for Research on Cancer published an authoritative treatise on cancer risks, ''Tobacco Smoke and Involuntary Smoking.''[5] It confirmed the cancer sites previously linked to active smoking: the lung, oral cavity, pharynx, larynx, esophagus, pancreas, urinary bladder and renal pelvis. As new smoking-related sites, it declared the nose, stomach, liver, kidney (renal cell), uterine cervix and bone marrow (myeloid leukemia). This volume pointed out that the risks for the previously recognized sites ranged from 3 for pancreatic cancer to greater than 20 for lung cancer; the risks for new sites were described to range generally from 2- to 3-fold. A causal link for involuntary smoking was declared for lung cancer, ranging from 20–30% for spouses and 12–19% for workplace exposure.[5] A total of 23 lung cancer studies on involuntary exposure through parental smoking were cited; 3 of them reported an increased risk for nonsmoking offspring. However, the data were considered inconclusive because of unreliable exposure assessment. Data on involuntary smoking and risks at other cancer sites were also reviewed, but they were inconsistent. The document stated that any effects of passive smoking should be reproduced at a higher magnitude in active smokers. The evidence for the risk of childhood cancer caused by maternal smoking was considered inconclusive; similarly, the evidence for effects through paternal smoking was inconclusive. A review of childhood cancers has reached an identical conclusion.[6]

In our study, we examine cancer risks in 0–70-year-old offspring of mothers and fathers who were diagnosed with lung cancer, using the nationwide Swedish Family-Cancer Database. Our hypothesis is that vulnerability to smoking-related cancers may span from the embryonic period through to adulthood. The exposure of offspring may be transplacental, through mother's milk or passive smoke during childhood. In accordance with the above treatise, we only consider organs known to be target sites in active smokers. We have no smoking data on any of the subjects, but lung cancer in parents serves as a proxy for their likelihood of smoking. Affected parents may represent a subgroup of heavy smokers or those genetically vulnerable to the effects of smoke. Their offspring may have inherited some of the risk factors and may be sensitive to tobacco carcinogenesis. It is likely that the familial risk for lung cancer, which is about 2.0, is partially explained by shared smoking habits among family members.[7] Thus, in analyzing cancer risks for offspring, we have no possibility to exclude the effects of their active smoking. However, we use age of onset and the relative magnitude of the effect in relation to lung cancer risks as reference points for possible inferences about cancer causation in offspring.

Material and methods

Statistics Sweden maintains a Multigeneration Register, whereby children born in Sweden in 1932 and later are registered with their parents (those pleading parenthood at birth) and organized as families.[8] Information on the Database is also available at the Nature Genetics website as ''Supplementary information.''[9] The data on families and cancers have a complete coverage, barring some groups of deceased offspring, which affect those born in the 1930s and who died before 1991. Although this small group of offspring with missing links to parents has negligible effect on the estimates of familial risk,[10] we limited our study to offspring whose parents were known, to eliminate possibility of bias. This Multigeneration Register was linked by the individually unique national registration number to the Cancer Registry from years 1958–2002. Cancer registration is currently considered to be close to 100%.[11]

The site of cancer is registered based on a 4-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7). The ICD codes 162.0 and 162.1 were used for lung cancer (thus excluding pleural mesothelioma). The following ICD-7 codes were pooled for ''upper aerodigestive tract'' cancer codes 161 (larynx) and 140–148 (lip, mouth, pharynx), except for code 142 (salivary glands). The 4-digit code was used to separate renal cell (1800) and pelvic (1801) cancer and to identify myeloid leukemia.

Standardized incidence ratios (SIRs) were used to measure cancer risks for offspring when their mother, fathers or both parents were diagnosed with lung cancer. The reference rate was calculated for offspring whose parents had no lung cancer. SIR was the ratio of the observed (O) to expected (E) number of cases. The expected numbers were calculated from 5-year standardized rates

Grant sponsor: Deutsche Krebshilfe; Grant sponsor: Swedish Cancer Society.
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E-mail: K.Hemminki@dkfz.de
Received 6 April 2005; Accepted after revision 10 June 2005
DOI 10.1002/ijc.21387
Published online 10 August 2005 in Wiley InterScience (www.interscience.wiley.com).

for age, sex, period (10-year bands), area (county) and socioeconomic status. Confidence intervals (95% CI or 99% CI) were calculated assuming a Poisson distribution.[12] Follow-up was started for each offspring at birth, immigration or January 1, 1958, whichever came latest. Follow-up was terminated on diagnosis of first cancer, death, emigration or the closing date of the study, December 31, 2002. In alternative analyses, the follow-up was started on January 1, 1990. The shorter follow-up period was used to control the findings because the data were more homogenous and because the majority of cancers in offspring of parents with lung cancer were recorded in this period.

Results

The Family-Cancer Database covered the years 1958–2002 from the Swedish Cancer Registry, and it included 17,693 mothers and 41,838 fathers with lung cancer. A total of 173,715 cancers were recorded in 0–70-year-old offspring. Table I presents age-specific SIRs for cancers linked to active smoking in offspring whose mothers were diagnosed with lung cancer compared to those whose mothers had no lung cancer. The SIRs are bolded and underlined if the 95% CIs or 99% CIs, respectively, do not include 1.00. Among offspring of any age, increased risks were observed for upper aerodigestive tract (SIR 1.45, 95% CI 1.06–1.94), nasal (2.93, 1.05–6.42), lung (1.71, 1.41–2.05) and bladder (1.52, 1.17–1.93) cancers; the risks for lung and bladder cancers were significant at <1% level. Kidney cancer was significantly increased (6.41, 1.67–16.58) in the age group 20–30 years. Even bladder cancer showed a significant increase (2.82, 1.34–5.20) in age group 30–39 years, earlier than lung cancer (first significant increase in age group 40–49 years). Only one cancer was diagnosed before age 20 years. The above results were essentially identical for the diagnostic period 1990–2002, and the essential data for lung, nasal and bladder cancers are shown in Figure 1.

Table II shows similar analysis for offspring of fathers with lung cancer. The age group of the first significant increase for lung cancer, 40–49 years, matched the one for offspring of mothers with lung cancer. The risk for pancreatic cancer of 1.64 (1.31–2.02) was only second to the risk for lung cancer (1.92, 1.73–2.12). The SIR for nasal cancer was 1.44 (0.61–2.84). When the analysis was repeated for a diagnostic period 1990–2002, the results were essentially identical (Fig. 1).

The risk for offspring was also analyzed when both parents were diagnosed with lung cancer. The risk for offspring lung cancer was 5.92 (n = 14, 95% CI 3.22–9.95). However, the numbers of other cancers relevant to our study were too few to be informative.

According to the previous data, smoking is associated with renal cell and pelvic cancers.[5] An inspection of the anatomic sites and histology of the 4 kidney tumors that were in excess among 20–29-year-old offspring (Table I) revealed that 3 were renal cell carcinomas (SIR 5.9, 1.11–17.46) and 1 was a papillary tumor in the renal pelvis. For a uniform classification, nasal cancer anatomic sites and histologies were inspected in the period 1990–2002. The SIR for nasal cancer among all 12 offspring whose parents were diagnosed with lung cancer was 2.17 (1.12–3.80). The risks were above unity for nasal cavity (SIR 2.11, 7, 0.84–4.37) and sinuses (SIR 3.16, 4, 0.82–8.17). The risk for squamous cell carcinoma was 2.45 (6, 0.88–5.36) and for adenoid cystic carcinoma 7.73 (3, 1.46–22.87).

Discussion

The ability of tobacco smoke to cause cancer in diverse organs is obviously related to different mechanisms.[13,14] The upper and lower respiratory system directly receives all inhaled ingredients of smoke, and the particulate and irritant material cause leukocyte recruitment, increased mucus production and chronic inflammation.[15] Part of the particulate material is cleared by swallowing, whereby it enters the gastrointestinal tract. Soluble carcinogens are

TABLE I – STANDARDIZED INCIDENCE RATIOS (SIR) FOR CANCER IN OFFSPRING OF MOTHERS WITH LUNG CANCER BY AGE AT DIAGNOSIS

Offspring cancer site	0–19 years			20–29 years			30–39 years			40–49 years			50–70 years			All		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive	0			1	0.93	0.00 5.32	3	0.99	0.19 2.93	15	1.66	0.93 2.75	26	1.49	0.97 2.18	45	**1.45**	1.06 1.94
Oesophagus	0			0			0	0.00		2	1.49	0.14 5.49	8	1.37	0.58 2.71	10	1.36	0.65 2.50
Stomach	0			0			3	1.64	0.31 4.85	6	1.06	0.38 2.33	15	1.28	0.71 2.12	24	1.22	0.78 1.82
Liver	0			0			0	0.00		1	0.26	0.00 1.46	12	1.03	0.53 1.81	13	0.76	0.40 1.31
Pancreas	0			0			0	0.00		6	1.50	0.54 3.28	17	1.26	0.73 2.02	23	1.25	0.79 1.88
Nose	0			0			1	3.08	0.00 17.63	2	3.33	0.31 12.25	3	3.14	0.59 9.29	6	**2.93**	1.05 6.42
Lung	0			1	1.50	0.00 8.61	5	1.86	0.59 4.38	31	**2.01**	1.36 2.85	80	**1.62**	1.28 2.01	117	**1.71**	1.41 2.05
Cervix	0			9	1.09	0.49 2.08	18	0.82	0.49 1.30	25	**1.56**	1.01 2.30	5	0.72	0.23 1.70	57	1.07	0.81 1.39
Kidney	1	0.65	0.00 3.72	4	**6.41**	1.67 16.58	3	1.20	0.23 3.56	9	1.11	0.50 2.11	17	0.92	0.54 1.48	34	1.09	0.75 1.52
Bladder	0			3	2.03	0.38 6.02	10	**2.82**	1.34 5.20	15	1.37	0.76 2.26	38	1.39	0.99 1.91	66	**1.52**	1.17 1.93
Myeloid leukemia	0			2	0.91	0.09 3.34	2	0.62	0.06 2.30	5	1.30	0.41 3.05	9	1.72	0.78 3.28	18	1.12	0.66 1.77

Bold type, 95% confidence interval (CI) does not include 1.00; underline type, 99% CI does not include 1.00; O, observed.

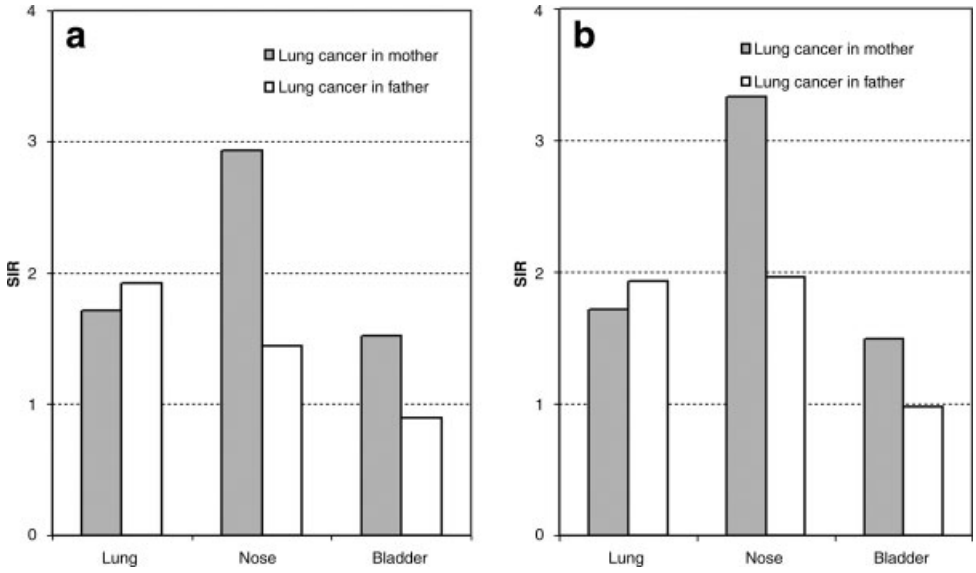

FIGURE 1 – Standardized incidence ratios (SIRs) for lung, nasal and bladder cancers in offspring of female (gray bars) and male (white bars) lung cancer patients in the whole follow-up period 1958–2002 (*a*) and last period 1990–2002 (*b*).

absorbed throughout the respiratory tract and attack distant organ systems. The mechanisms for organ specificity of tobacco carcinogenesis are not well understood, but obviously factors such as type, timing, duration and quantity of the carcinogenic challenge are important.[5] Some of the most controversial areas of tobacco carcinogenesis are the effects of passive smoking and exposure *in utero* and through breastfeeding, subjects of our study. A recent study on fetal chromosomes and maternal smoking concluded that smoking during pregnancy induces chromosomal instability.[16]

Most lung cancer patients are smokers, and in populations with long-term cigarette use, the population-attributable risk of smoking is thought to be up to 90%.[5] Probably only prospective data on smoking can reach higher levels of accuracy. Thus, one tenet of our study, using lung cancer in parents as a surrogate of their smoking habit, appears to be solid. Whether the mothers actually smoked during pregnancy is not known, and in Sweden pregnant women have reported reduced levels of smoking since the 1970s. According to the Swedish maternity register records, 31% of pregnant women smoked in 1983, but the percentage dropped to 13% in 1998 (www.sos.se). However, most of the present offspring with cancer were born well before information on smoking and risks for pregnancy were publicly known.[17] Rates of women breastfeeding their offspring were high before the 1960s, reaching a minimum at 31% in 1972 (recoded at 2 months) and then increasing to 62% after a few years of public promotion.[18]

Our main questions were whether *in utero* exposure and exposure through mother's milk or passive smoke during childhood from smoking parents would be a risk factor for cancers in adulthood. We would mechanistically infer that the affected sites should be recognized tobacco targets. However, the above questions are difficult to answer because we have no information on smoking habits of the offspring and because the available data show that smoking parents tend to have smoking children, through social and heritable causes.[19,20] The lack of smoking data is a disadvantage of our study, but the options are limited. A study inconclusively answering the questions that we posed to address here would be extremely complex and time consuming. The prospective Swedish maternity register has recorded smoking data since 1983,[21] but optimally biochemical confirmation of maternal smoking during pregnancy and breastfeeding should be carried out.[22] Moreover, the first Swedish birth cohort with information on maternal smoking reaches age 50 in the year 2033.

The present design has several merits, even beyond the size, high data quality (all diagnosis medically verified), nationwide coverage (all parent-offspring covered) and availability of data on potential confounding factors (socioeconomic group, period). There is strong evidence that familial risk of lung cancer is due to both heritable and environmental causes.[7,20] Thus in covering familial cases, by definition, the present subjects were sensitive to tobacco-related lung and other cancers, increasing the likelihood of observing effects. The SIRs measured between parental lung cancers and any offspring cancers would be elevated if there were genuine heritable causes for cancer susceptibility between the 2 sites. The Swedish Family-Cancer Database has been extensively used to explore familial clusters between cancer sites, including lung cancer.[23] The main associations found were between lung cancer and other tobacco-related sites, thus inconclusive about heritable etiology. What is important for our present interpretations is that all familial associations between lung cancer and other tobacco-related sites have always been much lower than concordant familial associations (lung-lung).

The observed lung cancer risk (1.92) for offspring whose fathers were diagnosed with lung cancer was consistent with a familial risk of lung cancer.[20,23] Increases were also found for other smoking-related cancers, such as upper aerodigestive tract (1.32) and cervical cancers (1.27). The relatively high risk of pancreatic cancer (1.64) compared to lung cancer cannot be explained because in active smokers these risks are about 3 and 20 or greater, respectively.[5] In offspring of female lung cancer patients, the risk of lung cancer (1.71) was not essentially different from offspring of male lung cancer patients; it has been suggested that a smoking father influences offspring's initiation of smoking more than mother's smoking.[24] The increase in upper aerodigestive tract cancers (1.45) was in line with that of lung cancer. However, the relatively high risk of nasal (2.83) and bladder cancers (1.53) cannot be explained by active smoking in offspring because the risks at these sites for active smokers are much smaller, 4 and 5, respectively, than the risk of 20 or greater for lung cancer.[5] The risk for bladder cancer was noted earlier than that of lung cancer, implying that the excess was not due to active smoking. Furthermore, the high risk of kidney cancer (6.41), including renal cell carcinoma (5.90) in an early-onset group (20–29 years), probably signals effects other than those of active smoking. Notably, the effects on the bladder and kidney were only observed in offspring of mothers with lung cancer. The IARC Working Group cited 3 studies that examined nasal cancer in nonsmoking spouses of smokers.[25–27] All these studies reported risks for spouses (2.55, 5.4 and 3.0) that were at the level of active smokers. In our present study, nasal cancer in offspring was in excess (2.17) even when either parent presented with lung cancer; the risk was particularly high (7.73) for adenoid cystic carcinoma histology.

TABLE II – STANDARDIZED INCIDENCE RATIOS (SIR) FOR CANCER IN OFFSPRING OF FATHERS WITH LUNG CANCER BY AGE AT DIAGNOSIS

Offspring cancer site	0–19 years			20–29 years			30–39 years			40–49 years			50–70 years			All		
	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI	O	SIR	95% CI
Upper aerodigestive	0			4	1.62	0.42 4.19	9	1.26	0.57 2.40	31	1.33	0.90 1.89	71	**1.34**	1.05 1.69	115	**1.32**	1.09 1.59
Oesophagus	0			1	11.74	0.00 67.30	0	0.00		1	0.31	0.00 1.78	25	1.39	0.90 2.05	27	1.25	0.82 1.82
Stomach	0			1	1.18	0.00 6.75	3	0.72	0.14 2.13	8	0.57	0.24 1.12	44	1.24	0.90 1.67	56	1.02	0.77 1.33
Liver	0			0			1	0.54	0.00 3.12	16	1.65	0.94 2.68	37	1.06	0.74 1.46	54	1.13	0.85 1.47
Pancreas	1	37.57	0.02 215.34	0			4	2.49	0.65 6.45	21	**2.14**	1.32 3.28	60	**1.47**	1.12 1.89	86	**1.64**	1.31 2.02
Nose	0			0			0			2	1.30	0.12 4.76	6	2.08	0.75 4.55	8	1.44	0.61 2.84
Lung	0			4	2.61	0.68 6.75	10	1.64	0.78 3.02	67	**1.75**	1.35 2.22	297	**1.97**	1.75 2.21	378	**1.92**	1.73 2.12
Cervix	0			23	1.21	0.76 1.81	66	1.24	0.96 1.58	56	**1.36**	1.03 1.76	25	1.24	0.80 1.83	170	**1.27**	1.08 1.47
Kidney	1	0.35	0.00 2.03	2	1.42	0.13 5.21	6	0.99	0.36 2.17	21	0.99	0.61 1.52	69	1.24	0.96 1.57	99	1.13	0.92 1.38
Bladder	1	1.56	0.00 8.93	3	0.85	0.16 2.53	8	0.91	0.39 1.80	26	0.89	0.58 1.31	75	0.89	0.70 1.11	113	0.89	0.74 1.07
Myeloid leukemia	2	0.64	0.06 2.35	1	0.21	0.00 1.23	7	0.97	0.38 2.01	7	0.70	0.28 1.45	11	0.69	0.34 1.24	28	**0.68**	0.45 0.99

Bold type, 95% confidence interval (CI) does not include 1.00; underline type, 99% CI does not include 1.00; O, observed.

The essential results of our study are summarized in Figure 1, showing the high relative risks in offspring of female lung cancer patients for nasal and bladder cancers both in the whole follow-up period 1958–2002 and the last period 1990–2002. We suggest that passive smoking during childhood contributes to nasal cancer risks because an excess was observed through lung cancer in either parent, though stronger through the mother. These findings are in agreement with the above cited nasal cancer studies on spouses. There is also strong evidence that passive smoking is causing middle ear infections and a number of respiratory effects, such as asthma, wheezing, coughing, bronchitis and impaired pulmonary function in children, in line with its activity on the respiratory epithelium.[28] The effects on the urinary bladder and the kidney are probably less related to passive smoking because the paternal contribution was nil. Rather, we assume that exposures *in utero* and through mother's milk are contributing to the effects observed on these target organs. Milk of smoking mothers contains high levels of nicotine, and urinary cotinine levels in infants may equal those of adult smokers.[29,30] Undoubtedly, many tobacco-derived carcinogens are able to pass to the fetus during pregnancy and to a nursing infant,[31] who has to excrete them through the kidney and the bladder; these rapidly growing organs may be particularly vulnerable.

The present data suggest that passive smoking during childhood is associated with an increase risk of nasal cancer, particularly of adenoid cystic carcinoma histology. For the excesses of bladder and kidney cancers, we propose a contribution of tobacco carcinogens that are transmitted through breastfeeding and *in utero* exposure. We admit that our inferences are based on indirect data, but we wish that they encourage more direct approaches, such as the recent chromosomal studies,[16] to address these questions of tobacco carcinogenesis with implications to the health of the offspring.

Acknowledgements

The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.

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